REMARKS

After entry of this amendment, the claims pending are claims 1, 2, 4-20, 22, 25, 26, 29-32, 37, 38, and 41-49. Claims 3, 21, 23, 24, 27, 28, 33-37, 39, and 40 are cancelled without prejudice. Claims 14, 22, 25, 26, 37 and 38 are amended as shown above. Claims 45-49 are new.

All amended and new claims are supported by the specification as follows. Claim 14 has been amended to clarify the subject matter of the invention and in supported by the specification at pages 6-8. Claim 22 has been amended to change is dependency only. Claims 25, 26, 37 and 38 have been amended to change their respective dependencies and grammatical phrasings. New claims 45-48 are supported, for example, at Example 24, specification pages 95-96. New claim 49 is supported by original claim 25 and elsewhere in the specification. No new matter is introduced by these amendments.

A. Double Patenting Rejections

The examiner rejects claims 1, 2 and 4-14 under this doctrine over claims 1-15 of issued US Patent No. 6,261,840, because the examiner considers the claims to be not patentably distinct from each other.

Claims 29-32 are provisionally rejected under this doctrine over claims 56-131 of copending Appln. No. 09/629,644 because the examiner considers the claims to be not patentably distinct from each other.

Applicants respectfully request reconsideration and withdrawal of this rejection in view of the submission of the two attached Terminal Disclaimers under 37 CFR §1.321(c). Applicants file these Terminal Disclaimers without addressing the substantive issues of obviousness, since grandparent US Patent No. 6, 261,840; copending parent Appln. No. 09/629,644, and the instant application have the same priority date and should terminate on the same date if the parent and instant applications issue as patents. In view of the attached terminal disclaimers, this rejection over the '840 patent and provisional rejection over the '644 application may be properly withdrawn.

B. Rejections Under 35 USC §112, second paragraph

Claim 14 is rejected under the second paragraph of Section 112 for use of the allegedly indefinite term 'active site'.

Applicants respectfully request reconsideration and withdrawal of this rejection in view of the above amendments to the claims and the following remarks. The term "active site" has been removed so that the claim reads "...-nucleobase portion of *the* nucleic acid *sequence* SEQ ID NO: 243, *wherein said hybridization modulates expression of PTP1B*. This description is supported in the original specification at page 6, lines 32 through page 7, line 2. It is respectfully submitted that this description of the portion of the target sequence that is targeted for hybridization by an antisense sequence of this invention must be a portion in which the hybridization provides the desired result.

C. Rejections Under 35 USC §112, first paragraph

Claims 15-28 and 33-44 are rejected under the first paragraph of §112 for lack of enablement of subject matter other than for the inhibition of mouse PTP1B comprising the i.p. injection of SEQ ID NO: 166 in a mouse Type 2 diabetes model. Specifically, the examiner does not agree with the claims for treatment of any condition associated with PTP1B.

Applicants respectfully request reconsideration and withdrawal of this rejection in view of the above amendments to the claims and the following remarks.

Claims 21, 23, 24, 27-28, 33-36 and 39-40 are cancelled. Claim 22 has been amended to depend from Claim 30, which is not subject to this rejection. Claim 25 has been amended to depend from Claim 32, which is not subject to this rejection. Claim 26 has been amended to depend from Claim 29, which is not subject to this rejection. These amendments and cancellations render this rejection moot as against those claims.

However, reconsideration of this rejection is requested as against pending claims 16-20, 22, 25, 26, 37, 38 and 41-44 for the following reasons. Claim 15 and its dependent claims 16-20 and 49 are fully enabled by the specification at Examples 22 and 23, which describe *in vitro* assays showing PTP1B inhibition by specific antisense oligonucleotides that hybridize to PTP1B and inhibit expression thereof. That these

claims may also encompass *in vivo* contacting is further supported, for example, by the description of the use of an illustrative PTP1B antisense oligonucleotide in Example 24. Reconsideration is also requested for Claims 41-44, as well as amended Claims 37 and 38 (which have been amended to depend from Claims 44 and 41, respectively) and for new claims 45-48 for the reasons discussed below.

In the specification, Applicants have provided in Examples 22 and 23 both the identity and use of antisense oligonucleotide sequences that target and hybridize to sequence (SEQ ID NO: 243) of human PTP1B and that demonstrate the ability to inhibit at least 40 % (and over 60% in some cases) of human PTP1B expression in *in vitro* assays. The assays used are similar to the *in vitro* assays in which the exemplary tested antisense sequence of SEQ ID NO: 166 inhibited the expression of rat PTP1B expression (see Example 16). While the exemplary sequence SEQ ID NO: 166 targeted a different PTP1B sequence (i.e., SEQ ID NO: 10), the functions of the claimed sequences were the same. All sequences inhibited PTP1B expression *in vitro* by binding to a target sequence of PTP1B. In fact, the binding of the antisense sequences to SEQ ID NO:243 caused greater inhibition of PTP1B than that demonstrated by the exemplary sequence. The fact that an antisense oligonucleotide that hybridizes to a PTP1B sequence and inhibits expression thereof in cells and tissue in vivo is demonstrated by Example 24, in which administration of an illustrative oligonucleotide inhibited PTP1B expression in monkey liver, adipose and muscle tissue. Therefore, claims 15-20, and 49 are clearly enabled by the present invention.

Independent Claim 29 and its dependent claims 22, 25, 26, and 30-32 are a method for decreasing blood glucose levels in animals using an antisense compound that is targeted to SEQ ID NO: 243, specifically hybridizes therewith, and inhibits expression of PTP1B. Independent Claim 41 and its dependent claims 37, 38, and 42-44 are a method of preventing or delaying the onset of an increase in blood glucose levels in animals by administering the above-described antisense compounds. Such therapeutic methods are supported in the specification by use of the same illustrative PTP1B antisense sequence that shares the function of inhibiting PTP1B expression by hybridizing to a PTP1B target sequence. The illustrative SEQ ID NO: 166 is shown to

lower blood glucose levels (Example 18) and decrease in plasma insulin levels in a diabetic animal model. The efficacy of this treatment was further demonstrated in Example 19, wherein it was established that such treatment reduced the mRNA expression of PTP1B. In fact the illustrative antisense sequence SEQ ID NO: 166 was selected as useful for further testing because it hybridized to its target sequence and demonstrated at least 30% inhibition of rat PTP1B expression (Example 16; page 85).

Additionally, Example 20 further demonstrates that inhibition of PTP1B by treatment with the antisense oligonucleotide also controls the weight gain of animal models for obesity (ob/ob) and diabetes (db/db), as well as for the control lean littermates. Example 24 provides evidence of the use of the illustrative antisense sequence to inhibit PTP1B expression, lower plasma insulin levels and increase insulin sensitivity in normal cynomulgus monkeys.

These results clearly demonstrate that *in vivo* treatment of animals, including primates in need of reductions in blood glucose and plasma insulin levels or control of body weight is enabled with the illustrative antisense oligonucleotide SEQ ID NO: 166.

The mouse model is an accepted clinical model for the demonstration of therapeutic efficacy in other mammals, particularly humans, for both diabetes (the db/db mouse) and obesity (the ob/ob mouse). For example, a brief review of the NCBI PubMed internet database produced a variety of publications employing these conventional models of disease. See, e.g., G. Wolf, **2001**, *Nutri. Rev.*, *59*(6):177-82; B. D. Rodgers *et al*, **2001** *J. Endocrinol.*, *168*(3):509-515; I. Stadler *et al*, **2001** *Lasers Surg. Med.*, *28*(3):220-6; D. Koya *et al*, **2000** *FASEB J.*, *14*(3):439-447. These documents demonstrate that the art accepts these mouse models as adequate representatives of the human conditions of diabetes and obesity. Such correlation of the mouse models with the human conditions is sufficient[1]. It is not a requirement for patentability that Applicants demonstrate clinical efficacy in every mammal, merely that one of skill in the art would accept the model as reasonably correlating to the condition. See, e.g., MPEP §2164.02.

---

[1] See, e.g., *In re Brana*, 51 F. 3d 1560,1566, 34 USPQ 2d 1436, 1441 (Fed. Cir. 1995)

In addition to the one monkey model of Example 24, the inventors have run additional experiments on obese, insulin-resistant hyperinsulinemic Rhesus monkey model and demonstrated again the plasma insulin lowering effects of the illustrative PTP1B antisense compound which increases insulin efficiency or sensitivity. This result further supports the results described in the other examples of the specification.

Thus, Applicants submit that the methods of this invention directed toward the lowering of blood glucose and plasma insulin, as well as the treatment of diabetes and obesity with antisense oligonucleotides to PTP1B that inhibit PTP1B expression, are clearly enabled by examples of the illustrative sequence.

Because the sequences recited in Claim 1 share with the illustrative sequence the *in vitro* ability to inhibit expression of PTP1B, as does the illustrative sequence, there is no reason to doubt that the similar functioning sequences that hybridize to SEQ ID NO: 243 of PTP1B should also share these similar *in vivo* functions.

Further, Applicants submit that the two cited references on antisense technology do not challenge the *in vivo* support for the amended claims. These references fail to provide any reasonable basis to doubt that the pharmacological activity reported in the animal models used in the instant invention would be similarly useful in the analogous human conditions.

S. T. Crooke (ed), Antisense Research and Application, (Springer-Verlag, Berlin, Germany 1998), pp1-50 (Crooke) is simply a review paper on the basic principles of antisense therapeutics. The author is merely stating a well-known fact in the development of any drug, not merely antisense. Data in cells are used routinely, however, as predictors of pharmacological activity in animals and humans. It is a fundamental principle of a drug development that data from whole cell studies, such as are provided in some of the Examples of the instant specification, are directly applicable to predicting *in vivo* activity. Moreover, in this case, the *in vitro* data is further confirmed by the above-discussed *in vivo* data. Crooke provides no reason to question the enabling disclosure of the *in vivo* data of the specification. In fact, statements by Crooke support the fact that development of antisense drug products in viewed by those of skill in the art as being the same as development of any other drug

product in terms of applying the basic principles of pharmacology. For example, on page 22, first paragraph, Crooke points out "...numerous well-controlled [pharmacological] studies have been reported in which antisense activity was conclusively demonstrated [in vitro] ." Crooke teaches that antisense oligonucleotides must be developed using well designed studies that progress logically from activity in cells to activity in animals in animals and humans.

Moreover, A. D. Branch **1998** *TIBS, 23*:45-50 teaches the need to develop antisense molecules based on sound data and careful screening, such as presented in the instant specification. Nowhere does the paper state that extrapolation from *in vitro* data to *in vivo* effects is unpredictable. Further, Branch provides no reason to question the legitimacy of the *in vivo* data presented in the present application for the treatment of diabetes, obesity, or to reduce the levels of glucose or insulin.

In view of this information, Applicants submit that this rejection may be withdrawn as against the pending and amended claims.

D. Rejections Under 35 USC §102(b)

Claims 1, 2 and 15 are rejected as anticipated under §102(b) by Huang *et al* 1998 *FASEB J.*, *12*(4):A188, Abstract 1099 (Huang) or either US Patent No. 5,726,027 (Olefsky). The examiner states that both references teach antisense inhibition of PTP1B.

Applicants respectfully request reconsideration and withdrawal of this rejection in view of the above amendments to the claims and the following remarks.

Huang is an abstract only that mentions use of a single 15 mer oligonucleotide against PTP1B and its use to knockout the activity of PTP1B in cells in culture. . Huang fails to identify the sequence that forms the target hybridization region of the PTP1B gene, i.e., it does not permit identification of SEQ ID NO: 243. Huang fails to disclose the exact sequence of this oligonucleotide, so Huang cannot be said to disclose an antisense sequence that binds SEQ ID NO: 243 as required by claim 1. Huang does not teach or suggest the methods of the pending and amended claims. Huang does not refer to *any* therapeutic use at all, much less the uses identified and

exemplified by Applicants, i.e., lowering blood glucose levels, treating diabetes or obesity, as now claimed by the pending method claims. Therefore, Huang cannot and does not anticipate the instant invention, as claimed.

Olefsky refers to antisense technology as a general tool for inhibiting expression of PTP1B DNA or RNA. Olefsky fails to teach or suggest the target regions of the PTP1B gene at all, much less SEQ ID NO: 243. Thus Olefsky cannot teach antisense sequences that bind to SEQ ID NO: 243 as recited by claim 1 and as used in the method claims of this invention. Olefsky fails to teach or suggest *any* therapeutic use at all, much less the uses identified and exemplified by Applicants, i.e., lowering blood glucose levels, treating diabetes or obesity, as now claimed by the pending method claims. Therefore, Olefsky cannot and does not anticipate the instant invention, as claimed.

Accordingly, withdrawal of this rejection against the pending claims is respectfully requested.

E. Rejections Under 35 USC §103(a)

Claims 1, 2, and 4-14 are rejected as obvious in view of Huang or Olefsky, in view of Chernoff *et al*, 1990, *PNAS, USA, 87*:2735-2739 (Chernoff); and further in view of Milner *et al*, 1997 *Nature, 15*:537-541 (Milner), and US Patent No. 5,801,154 (Baracchini). The examiner considers it obvious to design and use antisense molecules for the inhibition of PTP1B expression and incorporate modifications to these molecules, all assertedly taught by the cited art.

Applicants respectfully request reconsideration and withdrawal of this rejection in view of the above amendments to the claims and the following remarks.

The defects of Huang and Olefsky with regard to suggesting the pending claims are discussed above. No suggestions within the cited references, Chernoff, Milner or Baracchini are sufficient when added to the primary references to suggest the presently claimed invention.

Chernoff's disclosure of the cloning of a PTP1B contains no suggestion of antisense compounds targeted to any region of the PTP1B gene; i.e., it fails to identify or suggest SEQ ID NO: 243. Chernoff does not teach or suggest any specific

sequences for antisense compounds that bind to SEQ ID NO: 243, as required by claim 1 and the methods using the sequences of claim 1. Chernoff does not suggest any therapeutic use of ***any*** nucleotide sequence related thereto. Thus, Chernoff does not add anything to the primary references taken with the other secondary references that would make obvious the invention of the pending claims.

Milner's description of a screening technique similarly provides no suggestion which permits one to identify or suggest SEQ ID NO: 243 as a target PTP1B sequence for binding by the antisense sequences. Milner does not teach or suggest any specific sequences for antisense compounds that bind to SEQ ID NO: 243, as required by claim 1 and the methods using the sequences of claim 1. Milner does not teach or suggest a therapeutic utility of the sequences discussed therein. Thus, Milner does not add anything to the primary references taken with the other secondary references that would make obvious the invention of the pending claims.

Baracchini refers to modifications of antisense oligonucleotides in general, and specifically refers to multidrug resistance-associated protein (MRP), *not PTP1B.* Baracchini thus contains no disclosure that in any way suggests or refers to the methods of the present invention. Baracchini similarly provides no suggestion which permits one to identify or suggest SEQ ID NO: 243 as a target PTP1B sequence for binding by the antisense sequences. Baracchini does not teach or suggest any sequences for antisense compounds that bind to SEQ ID NO: 243, as required by claim 1 and the methods using the sequences of claim 1. Baracchini does not teach or suggest a therapeutic utility of the sequences discussed therein. Thus, Baracchini does not add anything to the primary references taken with the other secondary references that would make obvious the invention of the pending claims.

In view of the claim amendments and these remarks, Applicants submit that this rejection should be properly withdrawn as against the pending claims.

All rejections having been addressed and overcome, Applicants respectfully request that the pending claims be passed to issuance.

F. Information Disclosure Statement

Applicants submit herewith a Third Information Disclosure Statement and the fee associated therewith. Applicants further request that the Examiner consider the documents cited therein as well as the documents cited in the Second Information Disclosure Statement, filed December 4, 2002. Copies of the initialed, considered Forms 1449 are requested from the Examiner at her convenience. Applicants gratefully acknowledge receipt of the initialed Form 1449 pages from the original Information Disclosure Statement.

The Director is hereby authorized to charge any additional fees required with the filing of this paper or credit any overpayment in any fees to our deposit account number 08-3040.

Respectfully submitted,

HOWSON AND HOWSON
Attorneys for Applicant

By Mary E. Bak

Mary E. Bak
Registration No. 31,215
Spring House Corporate Center
Box 457
Spring House, PA 19477
(215) 540-9200